ARTICLE

Left frontal connectivity attenuates the adverse effect of entorhinal tau pathology on memory

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Abstract

Objective

To investigate whether higher global left frontal cortex (gLFC) connectivity, a putative neural substrate of cognitive reserve, attenuates the effect of entorhinal tau PET levels on episodic memory in older adults.

Methods

Cross-sectional ^{18}F-AV-1451 PET (to assess tau pathology), ^{18}F-AV-45 or ^{18}F-BAY94-9172 PET (to assess β-amyloid [Aβ]), and resting-state fMRI were obtained in 125 elderly participants from the Alzheimer's Neuroimaging Initiative, including 82 cognitively normal participants (amyloid PET-positive [Aβ+], n = 27) and 43 patients with amnestic mild cognitive impairment (Aβ+ = 15). Resting-state fMRI gLFC connectivity was computed for each participant as the average functional connectivity between the left frontal cortex (LFC) (seed) and each remaining voxel in the gray matter. As a measure of tau pathology, we assessed the mean tau PET uptake in the entorhinal cortex. In linear mixed-effects regression analysis, we tested the interaction term gLFC connectivity × entorhinal tau PET on delayed free recall performance. In addition, we assessed whether higher connectivity of the whole frontoparietal control network (FPCN), of which the LFC is a major hub, is associated with reserve.

Results

Higher entorhinal tau PET was strongly associated with poorer delayed free recall performance (β/SE = −0.49/0.07, $p < 0.001$). A significant gLFC connectivity × entorhinal tau PET interaction was found (β/SE = 0.19/0.06, $p = 0.003$), such that at higher levels of gLFC connectivity, the decrease in memory score per unit of entorhinal tau PET was attenuated. The FPCN connectivity × tau interaction was also significant (β/SE = 0.10/0.04, $p = 0.012$).

Conclusion

Both gLFC and FPCN connectivity are associated with higher resilience against the adverse effect of early-stage entorhinal tau pathology on memory performance.

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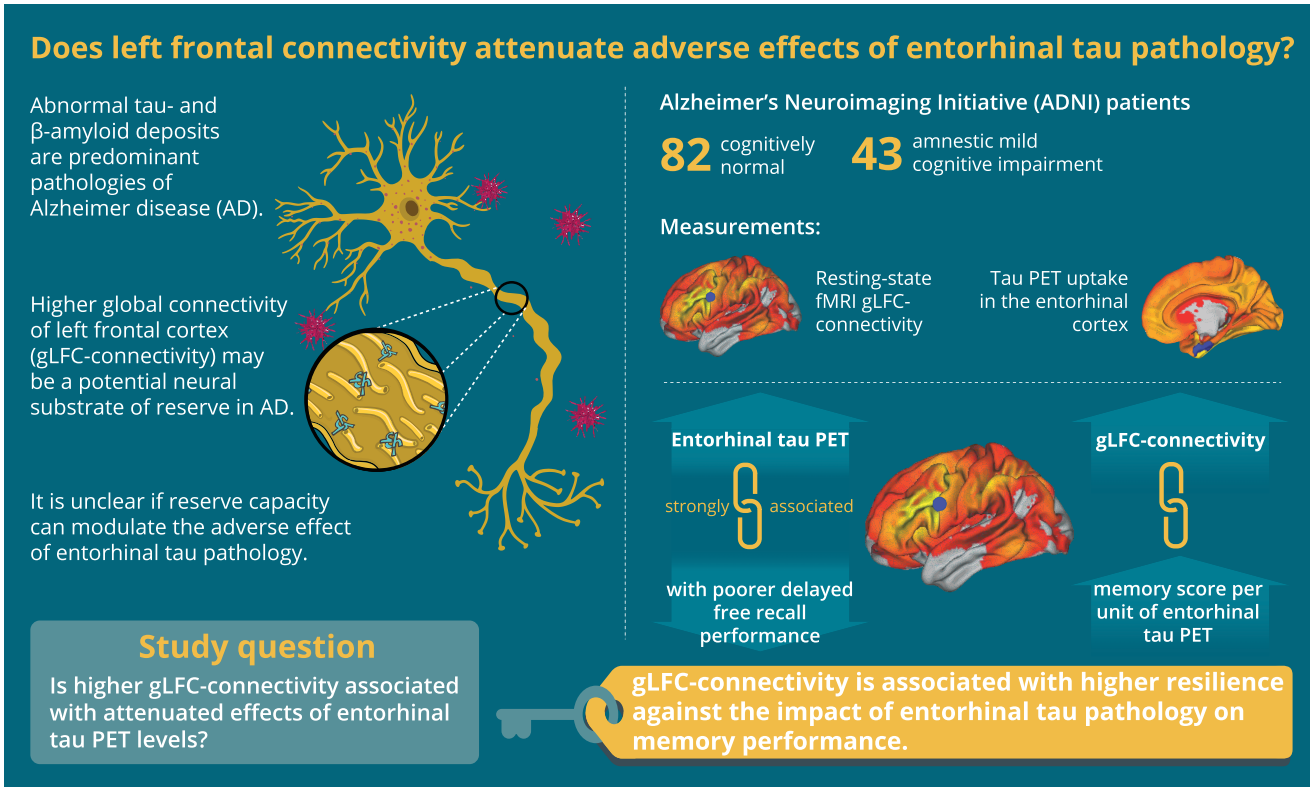
Glossary

AD = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **BOLD** = blood oxygenation level–dependent; **CDR** = Clinical Dementia Rating; **CI** = confidence interval; **CN** = cognitively normal; **EPI** = echoplanar imaging; **FPCN** = frontoparietal control network; **gLFC** = global left frontal cortex; **GM** = gray matter; **LFC** = left frontal cortex; **M1** = primary motor cortex; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **MNI** = Montreal Neurologic Institute; **PVC** = partial volume corrected; **RAVLT** = Rey Auditory Verbal Learning Task; **ROI** = region of interest; **SUVR** = standardized uptake value ratio; **TR** = repetition time; **WM** = white matter.



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Abnormal tau and β-amyloid deposition are the predominant primary pathologies in Alzheimer disease (AD), where pathologic tau particularly in the entorhinal cortex is associated with early episodic memory impairment.[1–4] However, reserve capacity may modulate the negative effect of primary AD pathology on cognitive performance, such that at higher levels of reserve, the cognitive impairment is alleviated.[5–8] While several environmental factors (e.g., education) have been associated with higher reserve,[9] the underlying brain mechanisms are largely unknown. We recently showed that higher global connectivity of the left frontal cortex (gLFC connectivity) assessed by resting-state fMRI is a potential neural substrate of reserve in AD.[10–13] That is, stronger connectivity between the left frontal cortex (LFC), a major hub of the frontoparietal control network (FPCN),[14,15] and any other brain region was associated with attenuated effects of gray matter degeneration on memory performance.[12,13]

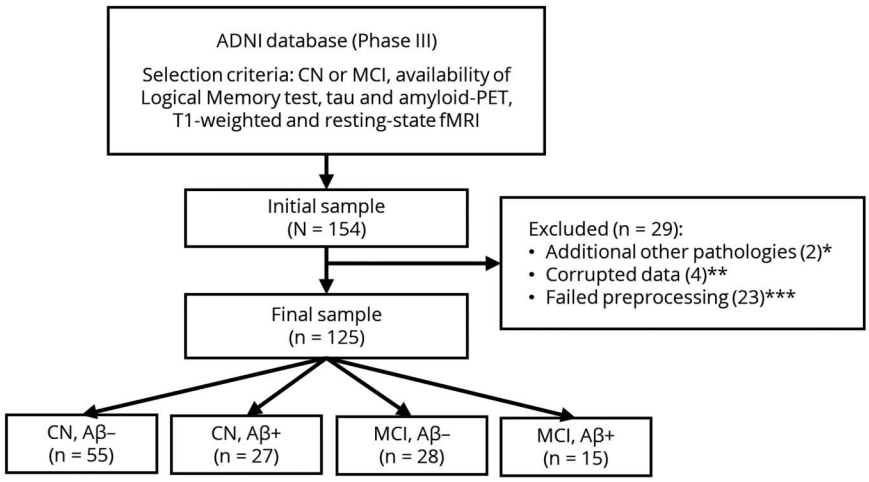
Whether reserve capacity modulates the adverse effect of entorhinal tau pathology remains unclear. Early postmortem studies suggested that reserve capacity may moderate amyloid but not tau pathology,[16–18] whereas more recent regional tau PET studies suggested higher reserve capacity to be associated with higher tolerance of tau PET.[19,20] However, in these studies, reserve was assessed only through nonspecific proxies including education or IQ, which lack mechanistic insight. Here, we examined gLFC connectivity and in addition functional connectivity of the whole FPCN as potential substrates of reserve. Given the central role of hubs in the brain, we hypothesized that in particular higher gLFC connectivity is associated with attenuated effects of entorhinal tau PET.

Methods

Participants

All participants were recruited within the Alzheimer's Disease Neuroimaging Initiative (ADNI; recruitment phase III, ClinicalTrials.gov ID: NCT02854033). Tau PET was introduced only in phase III of ADNI, with the total number of 258

Figure 1 Participant selection flowchart



*Excluded because of significant structural abnormalities. **Excluded because resting-state fMRI data had too few timepoints. ***Mainly excluded because of excessive head motion. Aβ = β-amyloid; ADNI = Alzheimer's Disease Neuroimaging Initiative; CN = cognitively normal; MCI = mild cognitive impairment.

participants (as of February 2018). Inclusion criteria for the current study beyond those of ADNI were diagnosis of either cognitive normal (CN) (Mini-Mental State Examination [MMSE] > 24, Clinical Dementia Rating [CDR] = 0) or amnestic mild cognitive impairment (MCI) (MMSE > 24, CDR = 0.5, objective memory loss on the education-adjusted Wechsler Memory Scale II, preserved activities of daily living). Moreover, availability of the following measures was required: episodic memory performance (Logical Memory subtest of the Wechsler Memory Scale), T1-weighted MRI and resting-state fMRI, tau PET, and amyloid PET, all obtained at the same study visit (figure 1 for schema of sample selection). From the total sample of 154 participants, who all satisfied the inclusion criteria, 29 participants were excluded (mainly due to poor data quality). The final sample included 125 participants, of which 82 were CN and 43 were MCI patients. Amyloid status was determined for all participants by applying established cutoffs for amyloid PET. Forty-two participants had been identified as amyloid-positive (CN/MCI = 27/15) and 83 participants as amyloid-negative (CN/MCI = 55/28) (see Assessment of amyloid status).

Standard protocol approvals, registrations, and patient consents

Ethics approval was obtained by the ADNI investigators. All study participants provided written informed consent.

Assessment of episodic memory

Episodic memory was measured as delayed recall performance from the Wechsler Memory Scale (Logical Memory subtest II, primary measure)[21] and the Rey Auditory Verbal Learning Test (RAVLT, secondary measure).[22] We focused on these tests of episodic memory since previous studies showed high sensitivity of these memory tests to entorhinal tau PET.[2,4] The secondary measure, RAVLT performance, was available in a subsample of 81 out of 125 participants.

MRI and PET acquisition

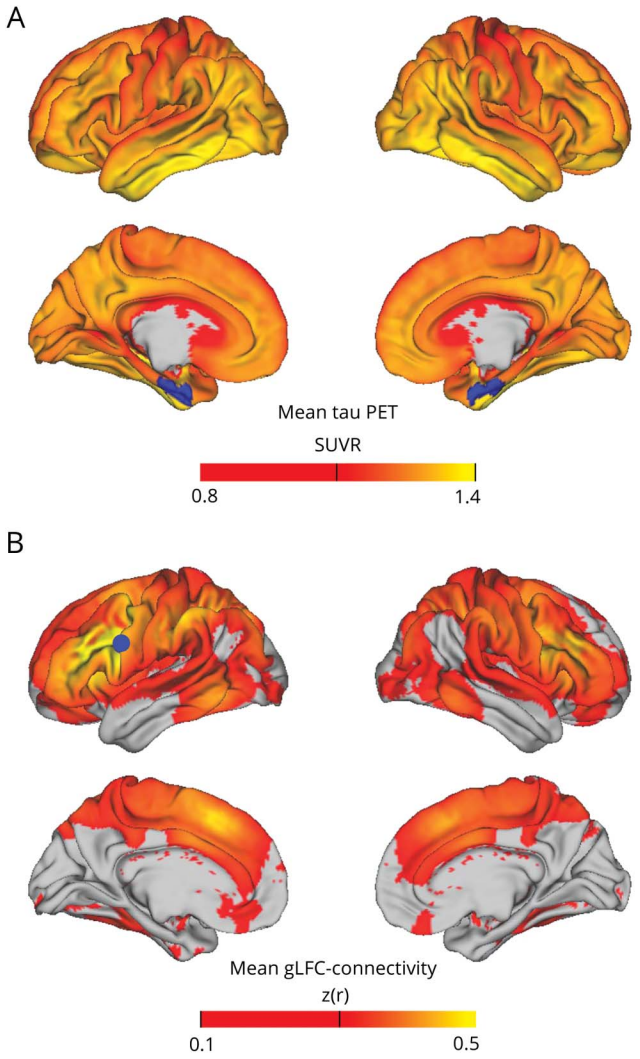
ADNI is a multicenter study, where MRI scans are obtained on different scanner systems from the manufacturers Siemens (Munich, Germany), GE (Cleveland, OH), and Philips (Best, the Netherlands) (n = 78/34/13) using unified scanning protocols (details can be found at adni.loni.usc.edu/wp-content/uploads/2017/07/ADNI3-MRI-protocols.pdf). In brief, structural MRI was recorded using a 3D T1-weighted magnetization-prepared rapid gradient echo sequence with 1 mm isotropic voxel resolution and a repetition time (TR) = 2,300 ms. For fMRI, a total of 200 volumes were recorded using a 3D echo-planar imaging (EPI) sequence in 3.4 mm isotropic voxel resolution with a TR/echo time/flip angle = 3,000/30/90°.

Tau PET was recorded 75–105 minutes postinjection of 370 MBq ^{18}F-AV1451, in 30-minute (6 × 5 minutes) time frames. Amyloid PET was recorded either 50 minutes postinjection of 370 MBq florbetapir or 90 minutes postinjection of 300 MBq florbetaben, for 20-minute (4 × 5 minutes) time frames. The dynamically acquired images were then realigned and averaged to obtain a single tau PET or amyloid PET image. Further details can be found online in the PET technical procedures manual (adni.loni.usc.edu/wp-content/uploads/2012/10/ADNI3_PET-Tech-Manual_V2.0_20161206.pdf).

Preprocessing of resting-state fMRI data

The same SPM12-based (Wellcome Trust Centre for Neuroimaging, University College London, UK) processing pipeline as described previously by us[10,11] was applied. In an initial step, structural MRI were segmented into gray matter (GM), white matter (WM), and CSF maps using SPM's new segment approach. The DARTEL toolbox implemented in SPM12 was used for high-dimensional nonlinear normalization of segmented images to Montreal Neurologic Institute (MNI) standard space.[23] Functional EPI images were slice-time corrected, motion corrected, coregistered to the T1 images, and DARTEL warped to MNI space. To further

Figure 2 Group-averaged distribution of tau PET imaging and seed-based global left frontal cortex connectivity



Surface renderings of (A) mean standardized uptake value ratio (SUVR) from [^{18}F]AV-1451 tau PET. The blue-colored entorhinal cortex mask was defined based on the Desikan-Killiany Atlas. Note that the entorhinal mask is displayed in Montreal Neurologic Institute space for illustration purpose only. The analysis was performed in native space using Freesurfer. (B) Whole-brain functional connectivity pattern from the left frontal cortex region of interest that is superimposed as a blue sphere on the left hemisphere.

denoise the EPI images, we regressed out nuisance covariates (i.e., average WM and CSF signal and motion measures estimated during EPI realignment), removed the linear trend, and applied band-pass filtering with a 0.01–0.08 Hz frequency band. To further minimize the influence of motion, which may compromise functional connectivity assessment,[24] we performed motion scrubbing, where we removed volumes that showed a frame-wise displacement of >1 mm, as well as 1 prior and 2 subsequent volumes. Only participants for whom fewer than 30% of volumes had to be removed were included in the current study.[10] Consistent with our previously applied analysis approach,[10] global signal regression was not part of the preprocessing pipeline. However, repeating the analyses with global signal regression applied yielded a consistent result pattern compared to that reported without global signal regression (data not shown).

Since ADNI participants were recruited in a multicenter framework using different MRI scanners, we additionally tested in this sample whether signal to noise ratio of the resting-state fMRI scans showed any differences between scanners in temporal signal to noise ratio using a previously described protocol.[25] Here, we found no significant differences when comparing signal to noise ratio between scanners using an analysis of variance ($p = 0.176$).

gLFC/FPCN connectivity analysis

gLFC connectivity was estimated for each participant based on fully preprocessed, GM-masked fMRI data and following our previously established protocol.[10,11] In brief, we created a binary sphere centered around the LFC (MNI: x = −42, y = 6, z = 28; Brodmann area 6/44; inferior frontal junction; figure 2B) with a radius of 8 mm, which was used as the seed region for connectivity analyses. The coordinates had been defined based on a meta-analytic approach (including over 428 task-fMRI studies on cognitive control) as previously described in detail.[10] Next, we calculated Fisher z transformed Pearson-moment correlations between the LFC region of interest time series and each remaining GM voxel. In order to obtain a gLFC connectivity score, we computed the average across all correlation values > 0 (i.e., higher LFC blood oxygenation level–dependent (BOLD) signal was associated with higher BOLD signal in a given GM voxel). Hence, a high gLFC connectivity score reflects high correlation strength, that is, high functional connectivity of that locus. Global functional connectivity was further computed for 2 unimodal control regions, which we did not expect to contribute to reserve, including one in the occipital pole (MNI: x = −19, y = −102, z = −3), as well as M1 in the motor cortex (MNI: x = −38, y = −22, z = 56). In addition, we assessed functional connectivity at the network level including 2 alternative indices of global FPCN connectivity: between-network or within-network connectivity of the FPCN. To this end, we used the well-established 17-netwok Yeo parcellation,[26] which identified 22 nodes as belonging to the FPCN. Mean Fisher z transformed correlation strengths between the time series of each FPCN node and all other nodes outside of the FPCN (for between-network connectivity) or all other nodes within the FPCN (for within-network connectivity) were calculated and then averaged for each FPCN connectivity index at the participant level.

Preprocessing of tau PET and assessment of entorhinal tau PET levels

For tau PET preprocessing, participant-specific tau PET images were coregistered to the corresponding high-resolution T1 image. Coregistered tau PET images were intensity normalized to the inferior cerebellar gray to obtain standardized uptake value ratio (SUVR) scores following previous recommendations.[27] Tau PET images were not partial volume corrected (PVC), since a recent investigation in a comparable

Table 1 Sample characteristics

	Total	CN, Aβ−	CN, Aβ+	MCI, Aβ−	MCI, Aβ+
Sample size	125	55	27	28	15
Age, y	73.5 (6.8)	72.6 (6.7)	74.3 (4.4)	74.9 (8.5)	72.8 (7.6)
Sex, F/M	73/52	31/24	19/8	15/13	8/7
Education, y	16.3 (2.7)	16.6 (2.3)	16.7 (2.7)	15.7 (3.2)	15.7 (3.2)
MMSE	28.7 (1.7)	29.1 (1.2)	29.4 (0.9)	28.1 (2.1)	27.1 (2.3)
Delayed recall, logical memory test	11.7 (5.0)	13.5 (3.3)	14.4 (3.7)	8.7 (4.5)	5.6 (5.5)
Word list learning, RAVLT[a]	5.3 (2.7)	5.7 (2.7)	6.7 (2.2)	4.3 (2.6)	3.8 (2.6)
Entorhinal tau PET, SUVR	1.16 (0.20)	1.10 (0.10)	1.17 (0.13)	1.18 (0.26)	1.38 (0.27)
Cortical amyloid PET, SUVR[b]	1.12 (0.22)	0.99 (0.05)	1.28 (0.16)	0.97 (0.12)	1.45 (0.23)
Amyloid status, −/+	83/42	55/0	0/27	28/0	0/15
Scanner, Siemens/GE/Philips	78/34/13	32/16/7	18/8/1	21/5/2	7/5/3

Abbreviations: Aβ = β-amyloid; CN = cognitively normal; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Task; SUVR = standardized uptake value ratio.
[a] Data of only 81 participants for whom RAVLT performance was available.
[b] Data of only 100 participants with the same amyloid (florbetapir) PET tracer.

group of ADNI participants showed no marked differences between results obtained with and without PVC.[2] However, we performed sharpening of the images, following a previously described protocol.[28] To this end, we used the output of T1-weighted image segmentation and discarded all coregistered PET voxels whose probability of being GM was lower than being CSF or WM.

Entorhinal tau pathology was quantified as the mean tau PET signal within individual entorhinal cortex masks within each participant's native space. In more detail, all T1-weighted scans were processed with FreeSurfer (v6.0; surfer.nmr.mgh.harvard.edu/). Within the Freesurfer standard pipeline (recon-all, default set of measures), left and right entorhinal cortex masks are computed based on the Desikan-Killiany atlas.[29] Superimposed on the coregistered tau PET images, these masks were used to compute a bilateral, mean entorhinal tau PET score for each participant (figure 2A illustrates the entorhinal cortex mask in MNI space). To account for potential effects of atrophy of the entorhinal cortices, Freesurfer-derived measures of entorhinal volume scaled by the total intracranial volume were considered as a covariate in the statistical analyses. Though entorhinal tau (Braak stage I) was the main focus of the present study, mean tau PET levels in limbic and neocortical regions were additionally assessed, in which higher tau levels indicate more advanced tau spreading according to the Braak neurofibrillary tangle staging scheme.[30] Details of the Braak staging procedure can be found elsewhere.[4] In brief, volume-weighted mean SUVR from 2 composite regions of interest (ROIs) was computed reflecting corresponding anatomical definitions of Braak stages III/IV (limbic) and Braak V/VI (neocortical). Tau levels in Braak stage II were intentionally not considered due to known off-target binding of the tau PET tracer in the hippocampus.[31] Instead, we assessed tau PET levels of the parahippocampal gyrus (Braak III), which had been shown to be relevant for memory besides entorhinal tau.[4]

Assessment of amyloid status

One hundred participants underwent ^{18}F-AV-45 (florbetapir) amyloid PET and 25 participants ^{18}F-BAY94-9172 (florbetaben) amyloid PET. Amyloid status was computed following a method described previously.[32] Amyloid PET images were coregistered to the corresponding T1-weighted image. Next, mean amyloid PET values were extracted from Freesurfer-derived GM regions (i.e., frontal, anterior/posterior cingulate, lateral parietal, lateral temporal) and intensity normalized to the whole cerebellum. All participants were stratified into amyloid-positive or amyloid-negative based on pre-established cutoffs (global florbetapir SUVR >1.11 or global florbetaben SUVR >1.2, table 1).[32]

Statistical analysis

First, mixed-effects regression analysis was conducted to assess whether entorhinal tau PET levels are a significant predictor of participants' delayed recall performance (Logical Memory Test of Wechsler Memory Scale) accounting for age, sex, diagnosis, and education as fixed effects and scanner as a random effect. The random effect in the current case was the type of scanner. In separate regression analyses, we tested whether inclusion of tau levels in brain regions of higher Braak stages, entorhinal volume, or amyloid status (or cortical amyloid PET) as fixed effects explained additional variance in delayed recall performance. For testing our main hypothesis, that is, higher gLFC connectivity attenuates the association between entorhinal tau PET and episodic memory

impairment, we tested whether there is a significant interaction effect of gLFC connectivity by entorhinal tau PET uptake on memory performance. A significant interaction would mean that the relationship between entorhinal tau PET levels and memory performance differs depending on the strength of gLFC connectivity. The model was controlled for age, sex, diagnosis, education, entorhinal volume, and amyloid status (fixed effects) as well as scanner (random effect). To test whether the gLFC connectivity × entorhinal tau PET interaction term improves the model fit, we compared the Akaike information criterion of the full model (with interaction term) to that of the reduced model (without interaction term). The Akaike information criterion is an estimate of the quality of a statistical model given a particular set of data.

The robustness of the interaction effect was tested by rerunning regression analysis after removing influential cases defined via Cook[33] distance D. Cook distance estimates the influence of single data points (cases) on the regression coefficient of a linear regression analysis, where the change in regression coefficient after exclusion of a given data point is tested. Data points with a large influence were excluded in order to test whether the regression coefficient is still significant (the cutoff for considering a case as influential was defined as [4/number of observations − number of independent variables − 1]).

In order to estimate exact confidence intervals (CIs) for the regression coefficient of the interaction term, nonparametric bootstrapping of the regression analysis described above was performed. For this purpose, we created 1,000 bootstrap samples by repeatedly resampling the original data (with replacement) and recorded the regression coefficient of the interaction term for each resampled dataset. The 95% CI of the regression coefficient was calculated, using the frequency histogram of the statistics computed from the bootstrap samples.

To ensure that any interaction effect of gLFC connectivity × entorhinal tau PET was not dependent on the particular memory test used as the dependent variable, we reran regression analysis, this time using word list learning on RAVLT as the dependent variable. To further ensure reliability of our results, we tested whether gLFC connectivity also interacts with tau PET levels in the parahippocampal gyrus. Furthermore, we tested whether connectivity of the whole FPCN network may moderate the association between entorhinal tau PET and episodic memory using the equivalent mixed-effect regression model as described above, but including the interaction term FPCN connectivity (either within- or between-network) × tau. As a test of specificity, we repeated this analysis for global connectivity of brain areas not related to cognitive control, but that are associated with motoric functions and visual perception (i.e., M1 and occipital pole), and for which we thus did not expect any interaction effect on the tau–memory relationship. In order to test whether the hypothesized interaction between gLFC connectivity × entorhinal tau was different between amyloid-positive and amyloid-negative participants, we extended the regression equation, additionally including the 3-way interaction gLFC connectivity × entorhinal tau PET × amyloid status on memory performance. A significant 3-way interaction would mean that the potential modulating influence global LFC connectivity has on the tau–memory relationship differs between amyloid-positive and amyloid-negative participants. Instead of amyloid status, we repeated the 3-way interaction analysis including continuous measures of mean cortical amyloid PET SUVR for the 100 participants who were assessed with the same amyloid (florbetapir) PET tracer. Finally, we tested in a regression analysis whether gLFC connectivity itself may decrease at higher levels of entorhinal tau PET or amyloid status controlling for age, sex, education, diagnosis (fixed effects), and scanner (random effect).

All analyses were performed using the freely available R statistical software package (r-project.org) (R Core Team, 2014); standardized beta coefficients were considered significant when meeting a p value <0.05.

Data availability statement

Data on participant demographics are available in table 1. Summary data of the statistical analyses are provided in table 2. ADNI data are accessible from adni.loni.usc.edu/data-samples/access-data/.

Results

Figure 2A shows the group-averaged SUVR derived from tau PET imaging, where higher values indicate more tracer uptake. In line with previous studies, marked tau accumulation was especially present in the inferior temporal, entorhinal, parahippocampal, and fusiform cortices (Braak I–III). Mean LFC connectivity across all participants is illustrated in figure 2B. Consistent with our previous findings,[10,11] higher activity in the LFC region was mainly associated with higher activity in frontal and parietal regions overlapping with the FPCN as well as the dorsal and ventral attention networks.

Entorhinal tau is a strong predictor of episodic memory

Higher entorhinal tau PET values were strongly associated with poorer delayed recall performance ($\beta = -0.38$, SE = 0.07, $p < 0.001$), while tau PET levels in regions corresponding to Braak stage III/IV ($p = 0.57$) or Braak V/VI ($p = 0.39$) did not explain any further variance in memory performance. Neither entorhinal volume ($p = 0.81$) nor amyloid status ($p = 0.43$) accounted for any variance after entorhinal tau PET had been included into the model. The same was true when continuous cortical amyloid PET levels were included (n = 100).

Higher gLFC connectivity attenuates the adverse effect of entorhinal tau PET on memory

Addressing our main hypothesis, we assessed whether higher gLFC connectivity is associated with an attenuated effect of entorhinal tau PET on memory. The interaction effect of

Table 2 Summary of linear mixed-effects models

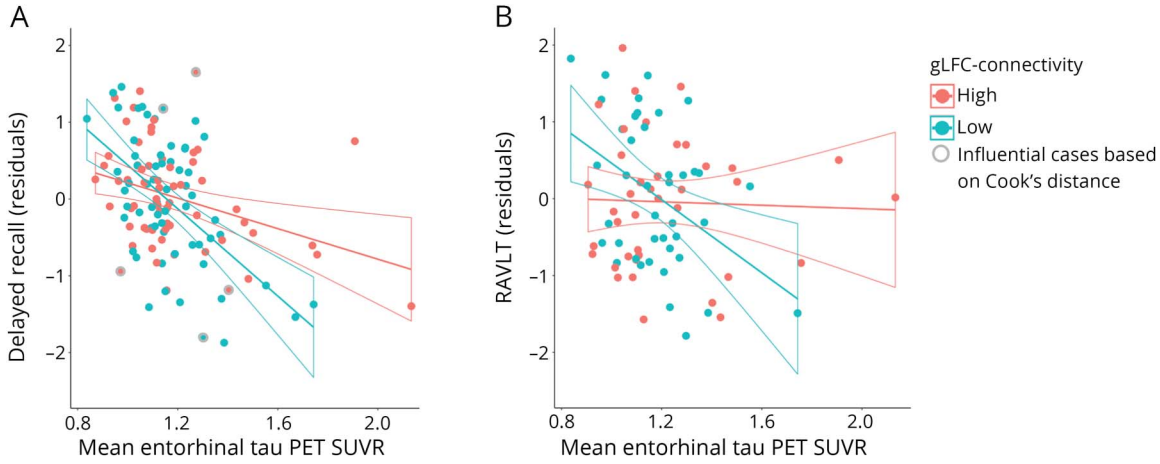
	β (SE)	T value	*p* Value	ΔR^{2c}	Overall R^{2d}
Reserve effect of gLFC connectivity[a]					
Entorhinal tau × gLFC connectivity	0.19 (0.06)	3.07	0.003	0.18	0.566
Entorhinal tau	−0.40 (0.07)	−5.67	<0.001	0.35	
gLFC connectivity	0.09 (0.06)	1.52	0.13	0.08	
Reserve effect of between-network FPCN connectivity[a]					
Entorhinal tau × gFPCN connectivity	0.09 (0.04)	2.61	0.010	0.16	0.554
Entorhinal tau	−0.40 (0.07)	−5.67	<0.001	0.35	
gFPCN connectivity	0.07 (0.06)	1.09	0.28	0.06	
Reserve effect of within-network FPCN connectivity[a]					
Entorhinal tau × lFPCN connectivity	0.10 (0.04)	2.56	0.012	0.15	0.574
Entorhinal tau	−0.41 (0.07)	−5.74	<0.001	0.35	
FPCN connectivity	0.08 (0.06)	1.29	0.20	0.06	
No reserve effect for control ROI, M1, and occipital pole[a]					
Entorhinal tau × M1 connectivity	−0.07 (0.08)	−0.82	0.41	0.03	0.527
Entorhinal tau × occipital connectivity	0.10 (0.06)	1.79	0.074	0.08	0.542
Influence of amyloid pathology[a]					
Entorhinal tau × gLFC connectivity × amyloid status	−0.03 (0.14)	−0.18	0.86	0.00	0.567
Entorhinal tau × amyloid status	−0.30 (0.14)	−2.21	0.029	0.12	
Amyloid status × gLFC connectivity	0.05 (0.07)	0.66	0.51	0.00	
gLFC connectivity is not affected by entorhinal tau or cortical amyloid PET[b]					
Entorhinal tau × amyloid status	−0.19 (0.19)	−0.99	0.32	0.09	0.083
Entorhinal tau	0.08 (0.13)	0.65	0.52	0.00	
Amyloid status	0.31 (0.20)	1.55	0.12	0.12	

Abbreviations: FPCN = frontoparietal control network; gLFC = global left frontal cortex; M1 = primary motor cortex; ROI = region of interest.
[a] Dependent variable: Delayed recall score of Wechsler Logical Memory Test.
[b] Dependent variable: gLFC connectivity.
[c] Squared semi-parietal correlation coefficient, which is the proportion of the total variance in the dependent variable that is uniquely explainable by each independent variable.
[d] Squared correlation coefficient, which is the proportion of the total variance in the dependent variable explained by all independent variables (i.e., the whole model).

gLFC connectivity × entorhinal tau PET on delayed recall performance was significant (β = 0.19, SE = 0.06, $p = 0.003$). Figure 3A shows that at higher levels of gLFC connectivity, the association between higher entorhinal tau PET and lower memory scores was attenuated compared to that at lower levels of gLFC connectivity (table 2). Residuals were normally distributed (Shapiro-Wilk normality test was not significant, $p = 0.80$). The bootstrapping-derived 95% CIs of the interaction term (β values) were 0.016–0.296. The full models including the interaction term showed a better model fit (i.e., Akaike information criterion) as compared to the reduced models (299 vs 303).

Robustness of the model was confirmed based on Cook distance. Five influential cases (see gray circle in figure 3A) had been identified showing Cook distance D larger than the cutoff (4/number of observations − number of explanatory variables − 1 = 0.055). After excluding the influential cases and rerunning the mixed effect model, the gLFC connectivity × entorhinal tau PET interaction effect remained significant (β = 0.20, SE = 0.06, $p = 0.001$). In order to ensure that the current results are robust across different tests of episodic memory, we repeated the mixed-effects regression analysis, this time using correctly recalled words on RAVLT as the dependent variable. Results showed a significant entorhinal tau × gLFC connectivity interaction effect on RAVLT performance (β = 0.20, SE = 0.10, $p = 0.039$, CI 0.085–0.381). Note that only those 81 participants could be included for whom RAVLT scores were available (figure 3B). No influential cases had been detected based on Cook distance. Robustness of the results was further supported by observing a significant parahippocampal tau ×

Figure 3 Interaction between entorhinal tau PET levels and global left frontal cortex connectivity (gLFC) on episodic memory performance



Tau PET levels in the entorhinal cortex are plotted against the residualized (A) delayed recall scores of the Wechsler Memory Scale and (B) word list learning on Rey Auditory Verbal Learning Task (RAVLT) (accounting for age, sex, diagnosis, education, and scanner). For illustrational purposes, groups of high and low gLFC connectivity (defined via median split) are plotted separately. The gray circles mark influential cases based on Cook distance. After removing them, the interaction between gLFC connectivity × entorhinal tau on delayed recall performance remained significant. Note that there are no influential cases in (B). SUVR = standardized uptake value ratio.

gLFC connectivity interaction on memory performance ($\beta = -0.14$, SE = 0.06, $p = 0.027$). Separate regression analyses with global functional connectivity of control ROIs including occipital pole and M1 as the independent variable instead of gLFC connectivity showed no interaction with entorhinal tau PET on memory performance (for occipital pole control ROI: $p = 0.074$; M1 control ROI: $p = 0.41$). Detailed results of all control analyses are summarized in table 2.

Reserve capacity of the whole FPCN

Since the LFC is part of the FPCN, we tested whether FPCN connectivity is also associated with reserve capacity against entorhinal tau PET levels. Mixed-effects regression analysis yielded a significant interaction between FPCN connectivity and entorhinal tau on memory (between-network connectivity: $\beta = 0.09$, SE = 0.04, $p = 0.010$; within-network connectivity: $\beta = 0.10$, SE = 0.04, $p = 0.012$). This result suggests that participants with high FPCN connectivity could maintain better memory performance compared to participants with lower FPCN connectivity at comparable levels of entorhinal tau PET burden.

Influence of amyloid pathology

We did not observe a significant gLFC connectivity by amyloid status interaction on delayed recall performance ($p = 0.51$). The 3-way interaction gLFC connectivity × entorhinal tau PET level × amyloid status on delayed recall performance was also nonsignificant ($p = 0.85$). These results did not change when cortical amyloid PET levels (n = 100) were considered.

gLFC connectivity is not significantly affected by tau PET or amyloid PET levels

Regression analyses testing the susceptibility of gLFC connectivity to AD pathology yielded no main effects of either entorhinal tau ($p = 0.52$) or amyloid status ($p = 0.12$) and also no tau × amyloid interaction effect ($p = 0.32$) on the strength of gLFC connectivity.

Discussion

The major finding of the current study shows that at higher gLFC connectivity levels the effect of elevated entorhinal tau PET on episodic memory impairment was attenuated. Additional exploratory analyses showed that FPCN connectivity was associated with a reduced association between entorhinal tau and memory decline. Together, these findings suggest that higher connectivity of the FPCN and in particular of its LFC hub contribute to resilience against the negative consequences of entorhinal tau accumulation on memory performance.

Our results contribute to the clarification of a key question on reserve capacity in relation to tau raised by previous findings. Previous histopathologic brain autopsy studies reported that education, that is, a proxy of reserve capacity, was predictive of relatively lower cognitive impairment in the presence of neuritic amyloid plaques but not neurofibrillary tangles,[16–18] suggesting that reserve capacity may fail to confer a cognitive benefit in the presence of more severe neurotoxic tau pathology. However, a recent tau PET study focusing on temporal lobe tau PET load suggested that higher IQ, another proxy of reserve, was associated with attenuated association between temporal lobe tau PET and global memory decline.[19] Furthermore, patients with AD with higher education showed more severe tau PET uptake, suggesting higher tolerance of tau PET pathology in individuals with higher education.[20]

These discrepancies between the early postmortem studies and more recent studies may stem from the different methodologic approaches (postmortem histopathology vs in vivo tau PET or differences in the location of brain regions assessed), and from the fact that education and IQ are nonspecific proxies of reserve, lacking insights into the functional brain mechanisms underlying reserve. The current hypothesis-driven study thus answers to the question raised by these previous studies, suggesting that resting-state fMRI assessed gLFC connectivity is a functional brain mechanism that enhances reserve capacity supporting memory abilities in the presence of entorhinal tau pathology.

For the marker of pathologic tau, we focused on tau PET uptake specifically in the entorhinal cortex since previous studies found the strongest correlations between episodic memory and tau PET levels in the entorhinal cortex.[2,4] Consistent with those results, we found that higher entorhinal tau PET was a close correlate of memory impairment. Of note, entorhinal volume or amyloid status did not add to the prediction of memory, suggesting that entorhinal tau pathology is a key determinant of memory impairment. We found no interaction between amyloid PET and gLFC connectivity on memory nor did amyloid levels modulate the interaction between gLFC connectivity and entorhinal tau on memory performance. While previous studies clearly suggest that the abnormal amyloid levels are associated with cognitive impairment,[34] the effect size is smaller compared to that of tau pathology.[35,36] Amyloid PET binds both to diffuse and neuritic plaques.[37] However, predominantly neuritic plaques have been found to be associated with cognitive impairment,[38] which possibly accounts for the weak association between amyloid PET and cognitive impairment. Together, these results support the importance of detecting reserve factors that may moderate the effect of regional tau pathology such as in the entorhinal cortex as a key pathology underlying memory impairment.

Our results on gLFC connectivity as a moderating factor of entorhinal tau pathology are consistent with our previous findings of higher gLFC connectivity to be associated with attenuated memory impairment at a given level of precuneus FDG-PET hypometabolism in prodromal AD and CSF tau across the AD spectrum.[10,11] Here, we additionally demonstrated that connectivity of the whole FPCN also attenuates tau-related memory impairment. These results suggest that the protective effects of gLFC hub connectivity can be generalized to the FPCN network level. The LFC is among the top 5% of all brain regions ranked by the degree of global connectivity,[39] and is a hub region of the FPCN.[14,15] Functional connectivity of the FPCN, and in particular, the LFC hub have been proposed to support higher cognitive functions[14] and to play a central role in mental health due to their central function of orchestrating the activity of other networks.[15,40] We have previously shown that higher gLFC connectivity is associated with higher efficiency of connected networks during memory task fMRI, and thus supports cognitive abilities.[12] In the current study, our exploratory analysis showed that global connectivity of the FPCN (including both between-network and within-network connectivity) was associated with an attenuated association between pathologic tau and episodic memory. The FPCN has been previously proposed to be a functional network that flexibly regulates the activity of other networks during changing task demands.[15] Thus, the FPCN and in particular its highly connected LFC hub may exert a central role in the brain to allow a flexible adjustment to cognitive challenges such as posed by pathologic brain alterations in AD. In this regard, it would be interesting for future studies to examine gLFC and FPCN connectivity in relation to cognitive control abilities, which are relatively preserved at least in early-stage AD.

A limiting factor of the present study is that cross-sectional data do not allow drawing conclusions on whether the gLFC connectivity profile is associated with future memory performance. The current results encourage future longitudinal studies to test whether individuals with higher gLFC connectivity experience less memory decline over time compared to participants with similar tau progression but lower gLFC connectivity. Another caveat is that in the current study focusing on tau PET not all brain pathology that may have influenced memory impairment could be captured. However, several observations and measures reduce the likelihood of that possible caveat. First, entorhinal tau PET was the main predictor of memory impairment in our regression analyses, since tau PET extracted from other brain regions and amyloid PET added no further value for predicting memory performance. Second, higher gLFC connectivity itself was not associated with tau PET or amyloid PET in the current study, suggesting that gLFC connectivity is not confounded by covarying levels of AD-related pathology. Another caveat is the unspecific binding of AV1451 PET, which may have affected the current results. Off-target binding has been shown to affect the meninges or choroid plexus, and may spill into the hippocampus.[31] We therefore did not include hippocampus tau PET in the current analysis in order to minimize the influence of off-target binding. Finally, at the cognitive level, a particular choice of episodic memory test may have influenced the results. However, we demonstrated that our findings were robust across different neuropsychological tests of episodic memory performance, supporting the construct validity of our results.

Overall, the current study demonstrated that higher gLFC connectivity attenuated the effect of elevated entorhinal tau on memory impairment. Together with our previous studies—demonstrating that gLFC connectivity moderates the negative consequences of AD-related brain abnormalities including FDG-PET hypometabolism and GM atrophy—gLFC connectivity and FPCN connectivity seem to play a broader role in supporting reserve in elderly participants.[41] Our results have clinical implications, suggesting that FPCN connectivity, and in particular gLFC connectivity, provides a target for therapeutic interventions via neurofeedback or

transcranial direct current stimulation.[42] The current results encourage future clinical trials to modulate frontoparietal connectivity as a strategy to enhance reserve capacity.

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Michael Ewers, PhD	ISD, Klinikum der Universität München, LMU, Munich	Author	Designed and conceptualized study, interpreted the data, drafted the manuscript for intellectual content

References

1. Bejanin A, Schonhaut DR, La Joie R, et al. Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. Brain 2017;140:3286–3300.
2. Maass A, Lockhart SN, Harrison TM, et al. Entorhinal tau pathology, episodic memory decline and neurodegeneration in aging. J Neurosci 2018;38:530–543.
3. Xia C, Makaretz SJ, Caso C, et al. Association of in vivo [18F] AV-1451 tau PET imaging results with cortical atrophy and symptoms in typical and atypical Alzheimer disease. JAMA Neurol 2017;74:427–436.
4. Schöll M, Lockhart SN, Schonhaut DR, et al. PET imaging of tau deposition in the aging human brain. Neuron 2016;89:971–982.
5. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychol Soc 2002;8:448–460.
6. Cabeza R, Albert M, Belleville S, et al. Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. Nat Rev Neurosci 2018;19:701–710.
7. Groot C, van Loenhoud AC, Barkhof F, et al. Differential effects of cognitive reserve and brain reserve on cognition in Alzheimer disease. Neurology 2018;90:e149–e156.
8. Ewers M, Insel PS, Stern Y, Weiner MW. Alzheimer's disease neuroimaging I: cognitive reserve associated with FDG-PET in preclinical Alzheimer disease. Neurology 2013;80:1194–1201.
9. Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. Psychol Med 2006;36:441–454.
10. Franzmeier N, Duering M, Weiner M, Dichgans M, Ewers M; Alzheimer's Disease Neuroimaging Initiative. Left frontal cortex connectivity underlies cognitive reserve in prodromal Alzheimer disease. Neurology 2017;88:1054–1061.
11. Franzmeier N, Düzel E, Jessen F, et al. Left frontal hub connectivity delays cognitive impairment in autosomal-dominant and sporadic Alzheimer's disease. Brain 2018;141:1186–1200.
12. Franzmeier N, Hartmann J, Taylor AN, et al. The left frontal cortex supports reserve in aging by enhancing functional network efficiency. Alzheimer's Res Ther 2018;10:28.
13. Franzmeier N, Hartmann JC, Taylor AN, et al. Left frontal hub connectivity during memory performance supports reserve in aging and mild cognitive impairment. J Alzheimers Dis 2017;59:1381–1392.
14. Cole MW, Yarkoni T, Repovš G, Anticevic A, Braver TS. Global connectivity of prefrontal cortex predicts cognitive control and intelligence. J Neurosci 2012;32:8988–8999.
15. Cole MW, Reynolds JR, Power JD, Repovs G, Anticevic A, Braver TS. Multi-task connectivity reveals flexible hubs for adaptive task control. Nat Neurosci 2013;16:1348.
16. Bennett DA, Wilson R, Schneider J, et al. Education modifies the relation of AD pathology to level of cognitive function in older persons. Neurology 2003;60:1909–1915.
17. Koepsell TD, Kurland BF, Harel O, Johnson EA, Zhou XH, Kukull W. Education, cognitive function, and severity of neuropathology in Alzheimer disease. Neurology 2008;70:1732–1739.
18. Roe CM, Xiong C, Miller JP, Cairns NJ, Morris JC. Interaction of neuritic plaques and education predicts dementia. Alzheimer Dis Assoc Disord 2008;22:188.
19. Rentz DM, Mormino EC, Papp KV, Betensky RA, Sperling RA, Johnson KA. Cognitive resilience in clinical and preclinical Alzheimer's disease: the association of amyloid and tau burden on cognitive performance. Brain Imaging Behav 2017;11:383–390.
20. Hoenig MC, Bischof GN, Hammes J, et al. Tau pathology and cognitive reserve in Alzheimer's disease. Neurobiol Aging 2017;57:1–7.
21. Wechsler D. A standardized memory scale for clinical use. J Psychol 1945;19:87–95.
22. Rey AL. Examen Clinique en Psychologie [Psychological Clinical Examination]. Paris: Presses Universitaires de France; 1964.
23. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage 2007;38:95–113.
24. Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage 2014;84:320–341.

25. Triantafyllou C, Hoge R, Krueger G, et al. Comparison of physiological noise at 1.5 T, 3 T and 7 T and optimization of fMRI acquisition parameters. Neuroimage 2005;26:243–250.
26. Yeo BT, Krienen FM, Sepulcre J, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 2011;106:1125–1165.
27. Baker SL, Maass A, Jagust WJ. Considerations and code for partial volume correcting [(18)F]-AV-1451 tau PET data. Data Brief 2017;15:648–657.
28. Jack CR Jr, Wiste HJ, Weigand SD, et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. Alzheimer's Dement 2017;13:205–216.
29. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006;31:968–980.
30. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991;82:239–259.
31. Marquié M, Normandin MD, Vanderburg CR, et al. Validating novel tau positron emission tomography tracer [F-18]-AV-1451 (T807) on postmortem brain tissue. Ann Neurol 2015;78:787–800.
32. Landau SM, Mintun MA, Joshi AD, et al. Amyloid deposition, hypometabolism, and longitudinal cognitive decline. Ann Neurol 2012;72:578–586.
33. Cook RD. Detection of influential observation in linear regression. Technometrics 1977;19:15–18.
34. Jansen WJ, Ossenkoppele R, Tijms BM, et al. Association of cerebral amyloid-beta aggregation with cognitive functioning in persons without dementia. JAMA psychiatry 2018;75:84–95.
35. Brier MR, Gordon B, Friedrichsen K, et al. Tau and Abeta imaging, CSF measures, and cognition in Alzheimer's disease. Sci translational Med 2016;8:338ra366.
36. Nelson PT, Alafuzoff I, Bigio EH, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. J Neuropathol Exp Neurol 2012;71:362–381.
37. Choi SR, Schneider JA, Bennett DA, et al. Correlation of amyloid PET ligand florbetapir F 18 binding with Abeta aggregation and neuritic plaque deposition in postmortem brain tissue. Alzheimer Dis Assoc Disord 2012;26:8–16.
38. Malek-Ahmadi M, Perez SE, Chen K, Mufson EJ. Neuritic and diffuse plaque associations with memory in non-cognitively impaired elderly. J Alzheimers Dis 2016;53:1641–1652.
39. Cole MW, Pathak S, Schneider W. Identifying the brain's most globally connected regions. Neuroimage 2010;49:3132–3148.
40. Cole MW, Repovš G, Anticevic A. The frontoparietal control system: a central role in mental health. Neuroscientist 2014;20:652–664.
41. Arenaza-Urquijo EM, Vemuri P. Resistance vs resilience to Alzheimer disease: clarifying terminology for preclinical studies. Neurology 2018;90:695–703.
42. Sole-Padulles C, Bartres-Faz D, Junque C, et al. Repetitive transcranial magnetic stimulation effects on brain function and cognition among elders with memory dysfunction: a randomized sham-controlled study. Cereb Cortex 2006;16:1487–1493.

Left frontal connectivity attenuates the adverse effect of entorhinal tau pathology on memory

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